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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

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EXAMINER

POPA, ILEANA

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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01/22/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/19/2008; 11/07/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 2, 3, 10, 11, 14, 21, 23, 24, 29-128, 130-134, and 143 have been cancelled.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending and under examination.

Response to Arguments

Double Patenting

3. Claims 1, 5-9, 12, 15-18, 22, 129, 135-137, 139-142 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, and 9-14 of copending Application No. 10/300,247 for the reasons of record set forth in the non-final Office action of 05/08/2008.

Applicant indicates that he defers rebuttal of the instant rejection until the cited co-pending application is allowed. Applicant's comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 103

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4. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,239,116, of record) in view of each Agrawal et al. (U.S. Patent No. 6,426,334, of record), Briles et al. (U.S. Patent No. 6,042,838, of record), Craig (U.S. Patent No. 6,689,757, of record), Kincy-Cain et al. (Infection and Immunity, 1996, 64: 1437-1440), and Berzofsky et al. (U.S. Patent No. 6,749,856) 247 for the reasons of record set forth in the non-final Office action of 05/08/2008. Applicant's arguments filed 11/07/2008 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the cited references fail to teach and it does not render obvious that CpG oligonucleotides, when administered by mucosal routes, induce a mucosal immune response. Applicant also argues that the cited art therefore also does not teach and it does not render obvious CpG administration to subjects in need of a mucosal immune response.

The Examiner states that Krieg et al. and Agrawal et al. both teach "a method of inducing a mucosal immune response in a subject". Applicant strongly disagrees. Applicant argues that neither Krieg et al. nor Agrawal et al. teaches mucosal immune response induction in subjects by administering CpG oligonucleotides. Applicant asserts that the Examiner does not identify where in either of these references such a teaching can be found. With respect to the Examiner's statement that it would have been obvious to substitute the oral administration route of Krieg et al. with the intranasal or rectal administration routes taught by Agrawal et al. because of "the predictable result of inducing mucosal immunity", Applicant argues that the Examiner incorrectly equates

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the IL-12 immune responses reported by Agrawal et al. with mucosal immune responses. With respect to Kincy-Cain et al. and Berzofsky et al. cited in support of this assertion, Applicant argues that neither of these references teach that an IL-12 immune response is a mucosal immune response. Applicant submits that Kincy-Cain et al. state that IL-12 can augment a mucosal immune response that arises after administration of intracellular pathogen *S. dublin*. The reference provides no data that evidence a relationship between IL-12 and mucosal immune response induction. Instead it infers effects of systemically administered IL-12 on mucosal immunity based on overall survival of the experimental subjects. The reference further speculates that IL-12 "most probably" exerts its effects through non-antigen-specific mechanisms including through IFN-gamma production by innate immune cells such as NK cells. Additionally, Applicant submits that Berzofsky et al. report that mucosal CTL immune responses are generated by administration to mucosal surfaces of soluble antigens or nucleic acids encoding such antigens. The reference does not teach that IL-12 must also be present in order to generate such mucosal immune responses although it contemplates administration of IL-12 presumably in order to augment a pre-existing mucosal immune response. Applicant argues that other references evidence that mucosal immune responses, as indicated by the presence of mucosal IgA, can exist in the absence of IL-12 and conversely that mucosal immune responses do not necessarily result from the presence of IL-12. For example, Applicant argues, Simmons et al. (J. Immunol. 2002, 168:1804-1812) reports that IL-12 knockout mice mount gut-associated IgA responses after infection with *C. rodentium* (Figure 6). The reference concludes that gut-associated IgA

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responses are not defective in IL-12 deficient mice. Arulanandam et al. (Vaccine 1999, 17:252-260) reports no change in lung IgA levels and suppressed fecal IgA levels in mice immunized intranasally with DNP-OVA with cholera toxin B subunit and IL-12. The reference therefore shows that IL-12 presence does not positively correlate with mucosal IgA levels. Marinaro et al. (J. Immunol. 1999, 162:114-121) documents that intranasal administration of IL-12 did not affect mucosal secretory IgA responses to oral or nasal vaccines. This reference too shows that IL-12 presence is not determinative of a mucosal immune response. Grdic et al. (Eur. J. Immunol., 1999, 29:1774-1784) compare the immunologic effects of cholera toxin (CT) and ISCOMs and report that while CT is an efficient inducer of a mucosal IgA response it did not induce detectable IL-12 at the protein and mRNA level. Conversely, the reference showed that although ISCOMs induced detectable IL-12 at the protein and mRNA level, it only poorly stimulated mucosal IgA production. Moreover, the reference reported that the capability of CT as mucosal adjuvant was unaffected in IL-12 knockout mice. It further concluded that "the immunomodulating ability of CT is independent of IL-12". Therefore, Applicant argues, these references refute the Examiner's position that an IL-12 immune response is equivalent to a mucosal immune response. Accordingly, there is no scientific basis for concluding that the immune responses of Agrawal et al. are mucosal immune responses. These references also refute that the IL-12 immune responses reported by Agrawal et al. are inherently mucosal immune responses should the Examiner be taking this position. Inherency, in this instance, requires that a mucosal immune response necessarily and inevitably result each and every time IL-12 is present. In re Robertson,

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169 F.3d 743,745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)("Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003). Applicant argues that the provided references clearly show this not to be the case. As a result, there is no evidence that the IL-12 immune responses of Agrawal et al. are inherently mucosal immune responses. Agrawal et al. and Krieg et al. do not teach mucosal immune responses following CpG oligonucleotide administration, either explicitly or inherently. In the absence of any teaching in either Krieg et al. or Agrawal et al. of a mucosal immune response, there is no evidence that such an immune response would be predictable, as indicated by the Examiner. There was no appreciation by either Krieg et al. or Agrawal et al. that CpG oligonucleotides could stimulate a mucosal immune response. In the absence of such an appreciation (or, in other words, knowledge), there can be no predictability. And in the absence of such knowledge, there cannot be obviousness, as obviousness is premised on what is known in the art. In re Kuehl, 475 F.2d 658 (CCPA 1973); In re Riickaert, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993) ("Obviousness cannot be predicated on what is unknown."). Applicant argues that the remaining references do not cure this deficiency. In particular, Craig does not cure this deficiency. In fact, Applicant argues, Craig teaches away from the rejected claims because Craig requires delivery of a nucleic acid that encodes an epitope (or antigen) while the rejected claims explicitly exclude such a limitation. Applicant argues that, although the Examiner counters that Craig is cited solely for the teaching of B-7 as a

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costimulatory molecule, the reference must be considered as a whole, including any disclosures that teach away from the rejected claims. MPEP 2141.03(VI); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984). The teaching in Craig of administration of a nucleic acid that encodes an epitope is not merely an alternative contemplated by Craig; it is a necessary feature of the teachings of Craig as a whole and as such cannot simply be disregarded by the Examiner. Importantly, it is a teaching that discourages a common limitation of the rejected claims, and thus it is therefore relevant to the issue of obviousness. In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Notwithstanding the deficiencies of Krieg et al. and Agrawal et al., the combination of these references with Craig yields a method that requires a limitation that is explicitly excluded from the rejected claims. Thus, additionally, the combination does not yield each and every limitation of the rejected claims. For these reasons, applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

Applicant argues that the cited art does not teach a method of inducing a mucosal immune response and provides references demonstrating that IL-12 is not necessarily linked to IgA production. In making these arguments, Applicant assumes that a mucosal immune response is only characterized by the induction of IgG. However, this assumption is not accurate. The prior art teaches that a mucosal immune response is also characterized by the induction of mucosal CTLs and that IL-12 acts as

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an adjuvant for induction of these mucosal CTLs (see Belyakov et al., Proc. Natl. Acad. Sci. USA, February 1998, 95: 1709-1714, Abstract, p. 1712, Fig.3; Berzofsky et al., Abstract, column 3, lines 1-9, column 12, lines 36-50). The prior art also teaches that a mucosal vaccine should encompass exogenous administration of IL-12 or a substance which stimulates IL-12 production (see Belyakov et al., p. 1713, column 1, first full paragraph; Kincy-Cain et al., p. 1439, column 2, last paragraph). Based on these teachings in the art as a whole, and since they teach their oligonucleotide as an IL-12 inducer, one of skill in the art would have known to use the oligonucleotide of Krieg et al. and Agrawal et al. in a method of inducing a mucosal immune response. The argument that Craig teaches away from the claimed invention is not found persuasive. The rejection is based on modifying Krieg et al. by further including the B-7 costimulatory molecule taught by Craig. The disclosure of a nucleic acid by Craig does not equal a teaching away. MPEP clearly states that a teaching away from the invention is a teaching which renders prior art unsatisfactory for the intended purpose (MPEP 2145 [R-6] X D). The mere exclusion of the limitation of nucleic acid from the claim does not render the combination of Krieg et al. and Craig unsatisfactory for the intended purpose of inducing a mucosal immune response. To teach away from the claimed invention, the art must indicate that using vaccines in conjunction with the B-7 costimulatory molecule would not result in a mucosal immune response. There is no such teaching in the art. For all these reasons, Applicant's arguments are not found persuasive and the rejection is maintained.

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New Rejections

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 8-12, 20-33, and 35 of copending Application No. 10/023,909, in view of Craig. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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The claims are obvious variants because all set of claims encompass a method of inducing mucosal immune response via administering to a subject a composition comprising an antigen, an oligonucleotide having the formula 5' X₁X₂CGX₃X₄ 3', wherein C is unmethylated and X₁, X₂, X₃, and X₄ are nucleotides, and a non-oligonucleotide adjuvant such as MPL. Although the application claims recite inducing an immune response and not inducing a mucosal immune response as recited in the instant claims, the application specification discloses that the immune response encompasses a mucosal immune response (see p. 45). The application claims do not recite further using B-7, as recited in the instant claim 25. Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the application claims by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

Thus, the patent claims and the application claims are obvious variant of one another.

Conclusion

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7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Belyakov et al. (Proc. Natl. Acad. Sci. USA, February 1998, 95: 1709-171) was cited in response to Applicant's argument that IL-12 does not play a role in inducing a mucosal immune response. Specifically, the reference teaches that IL-12 is involved in mucosal immune response and that a mucosal vaccine should encompass exogenous administration of IL-12 or a substance which stimulates IL-12 production.

8. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633